Is partial nephrectomy a better surgical option for the treatment of renal cell carcinoma?

"During the last decade, partial nephrectomy has become the standard of care for the treatment of T1 tumors. Nevertheless, partial nephrectomy is clearly underutilized."

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For many decades, radical nephrectomy (RN) has been the gold standard for the treatment of localized renal cell carcinoma (RCC). However, emerging evidence suggests that RN is a significant risk factor for the development of new-onset chronic kidney disease (CKD) or worsening of pre-existing CKD and leads to more cardiovascular events and worse survival [1–4]. Renal excision increases the risk factors for CKD by favoring arterial hypertension, proteinuria, hyperparathyroidism, anemia and metabolic acidosis. Patients are more likely to die of competing risks such as cardiovascular death than to die of the cancer itself. Owing to the higher risk of CKD following RN, the status of RN has been called into question. Other contributing factors are an increased incidental detection of small (<4 cm) renal masses with a significant proportion of benign tumors, the possibility of late recurrence of RCC in the contralateral kidney and the equal oncologic efficacy as partial nephrectomy (PN) for renal tumors less than 4 cm [5,6] and tumors between 4 and 7 cm [7,8]. A study in patients with localized RCC of 4 cm or less and a normal contralateral kidney showed that compared with PN, RN was associated with decreased overall survival (OS) in young patients (<65 years) with small renal masses [9].

"Although partial nephrectomy is a technically more complex operation than radical nephrectomy ... partial nephrectomy is safe with only a slightly higher complication rate than observed after radical nephrectomy."

With PN, one aims to save normal renal parenchyma to preserve renal function. Next to preservation of renal function and prevention of CKD, PN avoids the overtreatment of benign small renal masses. During the last decade, PN has become the standard of care for the treatment of T1 tumors [10]. Nevertheless, PN is clearly underutilized.

A study showed that the introduction of laparoscopic radical nephrectomy (LRN), a technically easier procedure in renal surgery coincided with a decrease in PN use [11]. In recent years, the use of PN has been gradually increasing. An initial significant concern with the use of PN treating RCC was the risk of local recurrence in the ipsilateral kidney due to incomplete resection. This concern may be tempered by the low rates of recurrence following PN in the literature (0–10%) and even lower (1–3%) when performing PN for tumors less than 4 cm [12]. A minimal normal tissue margin following PN is sufficient to avoid local recurrence [10,13]. The presence of positive margins after PN is a rare event and should be followed by more frequent and rigorous long-term surveillance [14,15]. In addition, positive surgical margins do not seem to negatively influence cancer-specific survival (CSS) [16,17].

Open PN (OPN) is the nephron-sparing modality with the largest clinical experience and the longest follow-up. A prospective, randomized Phase III study (EORTC 30904) has been conducted to compare RN and PN in 541 patients with tumors ≤5 cm and a normal contralateral kidney. Oncologic equivalence of PN and RN could not be definitively shown in this randomized study [18] but is seen in non randomized studies (5- and 10-year CSS rates up to 98.5 and 96.7%) [19] and is nowadays generally accepted. The percentage of patients with progression and renal cancer death in the randomized study is very small and cannot explain any possible OS differences between the two treatment arms [18]. A recent large population-based

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analysis of cancer control efficacy of PN versus RN in T1bN0M0 RCC showed that PN provides equivalent cancer control relative to RN [20]. Another recent study in patients with T1b renal tumors revealed that elective PN was associated with a significantly better OS than RN. This OS benefit seems to be attributable in part to prevention of postoperative CKD [21]. The same author showed in a retrospective study that PN was associated with better 5-year OS when compared with RN in patients with unanticipated benign tumors. This survival advantage appears to result partly from better preservation of estimated glomerular filtration rate (eGFR), but other unmeasured factors may also play a role [22]. Although PN is a technically more complex operation than RN, a previous report of the randomized study on surgical morbidity revealed that PN is safe with only a slightly higher complication rate than observed after RN [23]. A review of the literature revealed that in elective situations a better health-related quality of life is achieved with PN compared with RN because of a better preservation of renal function and overall quality of life [24]. Expanding the indications of elective OPN to larger, more complex or central tumors is associated with an increased but acceptable morbidity [25]. However, a study using a specific technique has demonstrated success in PN for central tumors with minimal intraoperative complications [26]. These data provide support for the use of PN in small renal tumors as first-line procedure whenever technically feasible, even in the presence of a normal contralateral kidney [10].

> "*Preserving nephrons should be the most important goal, whatever the surgical approach is, open or laparoscopic.*"

Laparoscopic partial nephrectomy (LPN) is becoming an accepted alternative to OPN. The oncological outcome in available LPN series with limited follow-up appears to be similar to the outcome achieved with OPN [27,28]. A recent study shows excellent and similar 7-year oncological outcomes after LPN and OPN [29]. During the development phase of LPN there have been initial concerns regarding the longer warm ischemia time (WIT) and higher risk of complications such as urinary leakage and hemorrhage [30]. Several specific operative modifications were developed to improve the laparoscopic techniques and the increased experience of laparoscopic surgeons during the last decade has resulted in a significantly reduced complication rate of LPN, which now seems similar to that of OPN [31–33]. A center with advanced laparoscopic expertise reported a mean WIT of less than 14 min, which is lower than or similar to that in more recent OPN series [31]. Hemostasis and warm ischemia remain the most important obstacles during LPN. A study compared the long-term impact of LPN and LRN on serum creatinine in patients with two normal kidneys on imaging and normal preoperative serum creatinine. Despite the warm ischemia and longer operative time, LPN preserves renal function better than LRN [34]. The eGFR is a better measure of renal function than serum creatinine. A recent study that used the Modification of Diet in Renal Disease (MDRD) equation to determine the eGFR in patients who underwent LPN showed that renal function impairment was more than twofold higher in patients with WIT of more than 40 min than in the other groups [35]. All attempts should be made to keep the WIT as short as possible and every minute counts when the renal hilum is clamped during PN [36]. Encouraging results with LPN and robot-assisted LPN have been reported for more challenging tumors, including small renal masses next to the renal hilum [37,38]. To date, OPN continues to be the preferred treatment for the management of RCC in centers without advanced laparoscopic expertise. It enables the fastest and safest nephron-sparing surgery, yielding the best preservation of renal function (WIT mostly around 10–15 min). It yields the same long-term oncological outcomes of RN for RCC. Also, in complex cases OPN will be successful, and a RN can thus be avoided. OPN is associated with minimal surgical morbidity. Bleeding is minimal and fistula is exceptional. Cooling, clamping and intraoperative ultrasound is easily applicable and the duration of surgery and WIT are shortest for open PN. The cost of technical tools used for open PN is very low. Laparoscopic and robotic techniques have to compete with the functional and oncological results of OPN.

A study in selected patients with locally advanced RCC showed that PN is safe and provides oncologic outcomes equivalent to patients managed with RN (CSS; 74 vs 78%, p = 0.113). The rate of procedure-related complications after PN was low (8.8%). Patients treated with PN had a similar estimated intraoperative blood loss, transfusion rate, and equal duration of surgery and hospital stay as patients managed with RN [39]. PN is the established treatment for T1a tumors (<4 cm) and an emerging standard treatment for T1b tumors (4–7 cm) provided that the

operation is technically feasible. The indications of PN are also expanding to more complex tumors. Adequate expertise and careful patient selection are important. RN remains a feasible option only when the tumor is not amenable to PN [10].

If RN is needed, LRN should be considered as it has become a recognized standard with more rapid recovery. However, to date, it is over-utilized in small renal tumors. Training in OPN should be continued and more frequent use is recommended. LPN is a technically challenging procedure with a long learning curve performed in specialized laparoscopic centers. Widespread training in LPN and robot-assisted laparoscopic techniques are needed and will extend the benefits of minimally invasive nephron-sparing surgery to a wider audience of patients and urological surgeons. When LPN expertise is not available or LPN encounters difficulties, PN use should be encouraged with conversion to OPN and not to LRN. Preserving nephrons should be the most important goal, whatever the surgical approach is, open or laparoscopic.

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